



Year: 2014

A Phase 1, Multicenter, Open-Label, First-in-Human, Dose-Escalation Study of the Oral Hedgehog Inhibitor Sonidegib (LDE225) in Patients With Advanced Solid Tumors

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Abstract: **PURPOSE:** This phase 1 trial was undertaken to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of the novel smoothened inhibitor sonidegib (LDE225), a potent inhibitor of hedgehog (Hh) signaling, in patients with advanced solid tumors. **EXPERIMENTAL DESIGN:** Oral sonidegib was administered to 103 patients with advanced solid tumors, including medulloblastoma (MB) and basal cell carcinoma (BCC), at doses ranging from 100 to 3000 mg daily and 250 to 750 mg twice daily, continuously, with a single-dose PK run-in period. Dose-escalations were guided by a Bayesian logistic regression model. Safety, tolerability, efficacy, PK, and biomarkers in skin and tumor biopsies were assessed. **RESULTS:** The MTDs of sonidegib were 800 mg daily and 250 mg twice daily. The main DLT of reversible grade 3/4 elevated serum creatine kinase (18% of patients) was observed at doses the MTD in an exposure-dependent manner. Common grade 1/2 adverse events included muscle spasm, myalgia, gastrointestinal toxicities, increased liver enzymes, fatigue, dysgeusia, and alopecia. Sonidegib exposure increased dose proportionally up to 400 mg daily, and displayed nonlinear PK at higher doses. Sonidegib exhibited exposure-dependent reduction in GLI1 mRNA expression. Tumor responses observed in patients with MB and BCC were associated with evidence of Hh pathway activation. **CONCLUSIONS:** Sonidegib has an acceptable safety profile in patients with advanced solid tumors and exhibits antitumor activity in advanced BCC and relapsed MB, which is strongly associated with activated Hh pathway, as determined by gene expression.

DOI: <https://doi.org/10.1158/1078-0432.CCR-13-1710>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-93120>

Journal Article

Accepted Version

Originally published at:

Rodon, Jordi; Tawbi, Hussein A; Thomas, Anne L; Stoller, Ronald; Turttschi, Christian P; Baselga, Jose; Sarantopoulos, John; Mahalingam, Devalingam; Shou, Yaping; Moles, Melissa A; Yang, Lin; Granvil, Camille; Hurh, Eunju; Rose, Kristine L; Amakye, Dereck D; Dummer, Reinhard; Mita, Alain C (2014). A Phase 1, Multicenter, Open-Label, First-in-Human, Dose-Escalation Study of the Oral Hedgehog Inhibitor

Sonidegib (LDE225) in Patients With Advanced Solid Tumors. *Clinical Cancer Research*, 20(7):1900-1909.
DOI: <https://doi.org/10.1158/1078-0432.CCR-13-1710>

Clinical Cancer Research



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Clin Cancer Res Published OnlineFirst February 12, 2014.

Updated version	Access the most recent version of this article at: doi: 10.1158/1078-0432.CCR-13-1710
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A Phase 1, Multicenter, Open-Label, First-in-Human, Dose-Escalation Study of the Oral Hedgehog Inhibitor Sonidegib (LDE225) in Patients With Advanced Solid Tumors

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Running title

Oral sonidegib (LDE225) in patients with advanced solid tumors

Keywords

Sonidegib (LDE225), smoothened inhibitor, hedgehog, medulloblastoma, basal cell carcinoma

Financial support

Supported by Novartis Pharmaceuticals Corporation for clinical studies and medical editorial assistance.

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Conflicts of interest

Melissa Moles, Lin Yang, Camille Granvil, Eunju Hurh, Kristine Rose, and Dereck Amakye are employees of Novartis. Melissa Moles, Camille Granvil, Eunju Hurh, Kristine Rose, and Dereck Amakye are stock owners of Novartis. Yaping Shou is a former employee of Novartis. Jose Baselga acted as a consultant/advisor for Novartis and received research funding from Novartis. Reinhard Dummer acted as a consultant/advisor for, and received honoraria from, Novartis. Jordi Rodon and Hussein Tawbi acted as consultants/advisors for Novartis. Anne

Thomas, Ronald Stoller, Christian P. Turtshi, John Sarantopoulos, Devalingam Mahalingam, and Alain Mita have no conflicts of interest.

Statement of Translational Relevance

Aberrant hedgehog (Hh) pathway activity has been linked to the pathogenesis of many cancers. The results of this phase 1 trial further advance the emerging clinical experience of Hh pathway inhibitors in patients with cancer. Oral sonidegib (LDE225) blocks the Hh pathway by selective inhibition of smoothened. Sonidegib exhibits an acceptable safety profile, exposure-dependent target inhibition, and clinically relevant antitumor effect in patients with locally advanced or metastatic basal cell carcinoma (BCC) and relapsed medulloblastoma (MB). The toxicities identified are manageable and reversible upon discontinuation of treatment. Furthermore, a five-gene Hh signature assay demonstrated a strong association between tumor responses and Hh pathway activation, thus supporting its use as a patient selection tool in future studies. These data support ongoing clinical investigations of sonidegib as a single agent in BCC and Hh pathway-activated MB, and as a combination partner with other agents in other malignant disease settings.

ABSTRACT

Purpose

This phase 1 trial was undertaken to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of the novel smoothened inhibitor sonidegib (LDE225), a potent inhibitor of hedgehog (Hh) signaling, in patients with advanced solid tumors.

Experimental Design

Oral sonidegib was administered to 103 patients with advanced solid tumors, including medulloblastoma (MB) and basal cell carcinoma (BCC), at doses ranging from 100 to 3000 mg daily and 250 to 750 mg twice daily, continuously, with a single-dose PK run-in period. Dose-escalations were guided by a Bayesian logistic regression model. Safety, tolerability, efficacy, PK, and biomarkers in skin and tumor biopsies were assessed.

Results

The MTDs of sonidegib were 800 mg daily and 250 mg twice daily. The main DLT of reversible grade 3/4 elevated serum creatine kinase (18% of patients) was observed at doses \geq the MTD in an exposure-dependent manner. Common grade 1/2 adverse events included muscle spasm, myalgia, gastrointestinal toxicities, increased liver enzymes, fatigue, dysgeusia, and alopecia. Sonidegib exposure increased dose proportionally up to 400 mg daily, and displayed nonlinear PK at higher doses. Sonidegib exhibited exposure-dependent reduction in GLI1 mRNA expression. Tumor responses observed in patients with MB and BCC were associated with evidence of Hh pathway activation.

Conclusions

Sonidegib has an acceptable safety profile in patients with advanced solid tumors and exhibits antitumor activity in advanced BCC and relapsed MB, which is strongly associated with activated Hh pathway, as determined by gene expression.

INTRODUCTION

The hedgehog (Hh) signaling pathway plays a key role during embryo-fetal development of the brain, bones, and muscles (1). During the postnatal period and adulthood, Hh pathway activity is involved in the regulation of bone development, tissue maintenance and repair, and maintenance of stem cell populations (hair follicles) (1, 2). Aberrant Hh pathway activation has been linked with the pathogenesis of many human cancers through Hh ligand-dependent and ligand-independent mechanisms.

Genetic alterations including loss-of-function mutations in the negative regulators Patched 1 (PTCH1) and/or Suppressor of Fused, or less frequently gain-of-function mutations in the positive regulator Smoothened (SMO), lead to ligand-independent pathway activation and have been linked to basal cell carcinoma (BCC), medulloblastoma (MB), and rhabdomyosarcoma (2). Overexpression of Hh ligand has been observed in pancreatic, colorectal, lung, breast, prostate, esophageal, and gastric tumors (2). Therefore, the Hh pathway has become an attractive therapeutic target. Inhibitors targeting SMO, including vismodegib, which is approved by the US Food and Drug Administration (FDA) for the treatment of metastatic or locally advanced BCC, are currently being investigated in clinical trials (3-9).

Sonidegib (LDE225), N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-40-(trifluoromethoxy)biphenyl-3-carboxamide, a novel selective inhibitor of SMO, was identified in a cell-based high-throughput screen (Supplementary Fig. S1) (10). Sonidegib demonstrated high tissue penetration (including blood-brain barrier) and good oral bioavailability in preclinical studies (10). Oral administration of sonidegib in mouse MB models *Ptch*^{+/-} *p53*^{-/-} and *Ptch*^{+/-} *Hic1*^{+/-} (hypermethylated in cancer 1) resulted in complete suppression of glioma-associated

oncogene homolog 1 (GLI1) and tumor regression, suggesting targeted inhibition of Hh signaling (11).

We report results from a first-in-human, dose-escalation, phase 1 study with sonidegib in adult patients with advanced solid tumors. The study population was enriched with patients with locally advanced or metastatic BCC and relapsed MB. This study established the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of continuous daily oral sonidegib administration. Additionally, safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity were assessed.

PATIENTS AND METHODS

Patient Population

Adult patients with histologically or cytologically confirmed advanced solid tumors, including MB, whose disease progressed despite standard therapy or for whom no standard therapy was available were eligible. Other key inclusion criteria were measurable or evaluable disease defined by Response Evaluation Criteria In Solid Tumors (RECIST 1.0) (12) or the Neuro-Oncology Criteria for Tumor Response (MB only) (13, 14) and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 . In addition, all patients must have had adequate bone marrow (absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$, hemoglobin $\geq 9 \text{ g/dL}$, and platelets $\geq 100 \times 10^9/\text{L}$), liver (serum total bilirubin $\leq 1.5 \times$ upper limit of normal [ULN] and aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ ULN or $\leq 5.0 \times$ ULN if liver metastases are present), and kidney function (serum creatinine $\leq 1.5 \times$ ULN or 24-hour creatinine clearance of $\geq 50 \text{ mL/min}$). Patients were excluded if they had a history of a brain tumor or brain metastases (except relapsed MB), clinically significant cardiac disease, or gastrointestinal

dysfunction that might impair sonidegib absorption. Treatment with strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9, which have a narrow therapeutic index, was prohibited during the study.

All patients provided written informed consent before enrollment. The study followed the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and local regulations (European Directive 2001/20/EC and US Code of Federal Regulations Title 21). The protocol and amendments were approved by the institutional review board, independent ethics committee, or research ethics board at each center.

Study Design

The primary objective of this dose escalation, multicenter, open-label phase 1 study was to determine the MTD and DLTs of oral sonidegib, administered on a continuous daily schedule. Additional objectives included safety, PK, PD, and antitumor activity. During dose escalation, all patients received a single oral dose of sonidegib in a 7-day PK run-in period to characterize the PK profile of sonidegib. Once the MTD was determined for the once-daily regimen, additional patients were enrolled to ensure a minimum of 22 patients were treated at the MTD to provide a 90% probability of detecting adverse events (AEs) with an incidence of 10% and permit further assessment of PK, PD effects, and antitumor activity. Twice-daily dosing was also tested to explore the effect of dose fractionation and MTD.

Sequential cohorts of patients were treated with escalating doses of sonidegib once (100, 200, 400, 800, 1000, 1500, or 3000 mg) or twice daily (250, 400, or 750 mg), continuously in a 28-day cycle. Twice-daily dosing was evaluated to address apparent solubility-limited absorption

at doses > 400 mg once daily. A minimum of three evaluable patients were required to make dose-escalation decisions after completing cycle 1. Additional patients were enrolled to allow for dropouts and to better define the safety, PK, or PD of sonidegib at a given dose. Enrollment of patients with MB and advanced BCC was allowed at previously well-tolerated doses during the dose-escalation phase.

A two-parameter Bayesian logistic regression model for escalation with overdose control was used to guide dose escalation decisions (15, 16). A DLT was defined as a significant AE or abnormal laboratory parameter adjudged to be Common Terminology Criteria for Adverse Events (CTCAE version 3.0) grade ≥ 3 in severity and considered unrelated to disease progression, intercurrent illness, or concomitant medications. The MTD was defined as the highest dose of sonidegib predicted to have < 25% probability of a DLT rate of $\geq 33\%$ during cycle 1 (first 28 days). After tolerating the assigned dose for at least two cycles, inpatient dose escalations were permitted. Dose-escalation decisions were impacted by the emergence of late-onset, reversible grade 3/4 elevated serum creatine kinase (CK), occurring primarily during cycle 2.

Safety Evaluations

Safety was assessed according to CTCAE version 3.0 guidelines (17). Assessments included regular laboratory evaluations, physical examinations, vital signs, weight, and periodic electrocardiogram recordings. All patients were monitored for safety from the first dose until 28 days after the final dose. Additional monitoring, including weekly serum CK during cycle 2 and on the first day of subsequent cycles, was implemented.

PK Assessments and Analyses

Blood Sample Collection and Handling—Blood samples for pharmacokinetic (PK) analyses were collected throughout the study. For the PK run-in period, serial blood samples were collected starting on day 1 (ending on day 5) at predose and 0.5, 1, 2, 4, 6, 8, 24, 48, 72, and 96 hours postdose. Serial blood samples were also collected on day 15 of cycle 1 at predose and 0.5, 1, 2, 4, 6, and 8 hours postdose. Blood samples were also collected predose on days 1, 8, 16, and 22 of cycle 1; days 1, 2, 8, 15, 16, and 22 of cycle 2; and day 1 of all subsequent cycles. Samples were processed and frozen at $\leq -70^{\circ}\text{C}$ within 90 minutes of the collection.

Preparation and Analysis of Plasma Samples—Plasma samples were prepared using a protein precipitation extraction procedure, and sonidegib concentrations were determined using a validated liquid chromatography (LC)/mass spectrometry (MS)/MS assay using an API 5000™ triple quadrupole mass spectrometer from AB Sciex (Foster City, CA, USA) equipped with an electrospray interface. Sample extracts were analyzed using gradient reverse-phase chromatography with a Capcell Pak C18 ACR, 150 × 4.6 mm ID, 5-μm particles (Shiseido Co Ltd, Tokyo, Japan). The mobile phase consisting of water/0.1% ammoniac solution followed by acetonitrile/isopropanol (8:2 vol/vol) was pumped through the column at a flow rate of 1.0 mL/min. Positive-ion multiple reaction monitoring (MRM) with a labeled internal control and a lower limit of quantitation of 0.0247 ng/mL (using 0.050 mL of plasma) was used for detection. The MRM transition monitored for sonidegib, and the labeled internal standard was m/z 486.07 to 428.08 and 490.07 to 432.08, respectively. The LC/MS/MS chromatograms of all analyzed baseline samples showed no interfering peaks, demonstrating selectivity of the method. Intraday and interday precision as represented by the coefficient of variation and accuracy as represented by the mean bias were within 20%. The validated method is suitable for the determination of sonidegib in human plasma.

PK Assessments—PK parameters were calculated using noncompartmental methods with WinNonlin[®], version 5.2 (Pharsight, Mountain View, CA, USA). Peak plasma concentration (C_{\max}) and time to reach C_{\max} (T_{\max}) were obtained from individual sonidegib concentration-time profiles. Area under the plasma concentration-time curve (AUC) values were calculated using the linear trapezoidal rule. Steady state was defined as a stable plasma trough concentration in at least two consecutive samples. Accumulation ratios were calculated by dividing the average plasma trough concentration at steady state by the trough concentration after the first dose.

Biomarker and Antitumor Evaluations

Fresh or archival tumor samples were collected when available, and biopsies of normal skin were collected from all patients before sonidegib treatment, at the end of cycles 1 and 2, and within 14 days after the last dose. RNA was extracted from tissue samples and analyzed by reverse transcriptase–polymerase chain reaction (RT-PCR) to measure GLI1 expression and Hh pathway activation status, based on the five-gene Hh signature assay (18, 19).

All potential sites of tumor lesions were evaluated by computed tomography, magnetic resonance imaging, or physical examination (locally advanced BCCs) at baseline and every 8 weeks. Antitumor activity was determined according to RECIST 1.0 (12) and the Neuro-Oncology Criteria of Tumor Response (MB only) (13, 14). [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in a subset of patients at baseline, day 28 of cycles 1 and 2, and post treatment to supplement RECIST assessments. Percent changes from baseline standardized uptake value (SUV) using the average over lesions per patient were determined for patients with at least one lesion ≥ 2 cm with a tumor-to-background ratio

of ≥ 2 . Metabolic partial response (PR) was defined as a decrease of $\geq 25\%$ in summed maximum SUV in the target lesion as per the recommendations proposed by Weber *et al* (20).

Statistical Analyses

Demographics, safety, efficacy, and relevant PK and pharmacodynamic measurements were summarized using descriptive statistics and contingency tables. Study data included all patient data from the dose-escalation and enrichment cohorts until all patients had completed at least three cycles of treatment or discontinued the study.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 103 patients, comprising 73 and 30 patients on the once-daily and twice-daily schedules, respectively, were enrolled between March 2009 and June 2011. Overall, 16 patients with BCC and nine patients with MB were treated. Primary tumor site, previous antineoplastic therapies, and ECOG performance status of patients enrolled are listed in Table 1.

Safety Findings

Sonidegib was generally well tolerated with typically mild (grade 1/2) AEs (Table 2). Patients comprising the dose-decision sets are listed in Supplementary Table S1. Most common treatment-related grade 1/2 AEs experienced by $> 10\%$ of patients included nausea, dysgeusia, anorexia, vomiting, muscle spasms, myalgia, increased serum CK, fatigue/asthenia, and alopecia, characterized by gradual thinning of the hair. Notable grade 3/4 AEs occurring in $< 5\%$ of all treated patients included weight loss, myalgia, hyperbilirubinemia,

dizziness, and asthenia. There were no deaths due to drug-related toxicities. Dose reduction occurred in 17 patients (17%), mostly treated at doses > 800 mg. Twenty patients (19%) permanently discontinued treatment because of AEs, mostly associated with CK elevation (14 of 20). Reversible grade 3/4 serum CK elevation was considered to be dose limiting in 19 patients (18%) at doses \geq 800 mg once daily and \geq 250 mg twice daily (Supplementary Table S1). These DLTs tended to occur 3 to 6 weeks after treatment initiation in an exposure-dependent manner (Fig. 1). Due to the delayed onset, reports of DLTs initially appeared to be limited to high-dose cohorts; however, after further evaluation in expanded cohorts, two of 26 patients and two of 14 patients experienced DLTs at 800 mg once daily and 250 mg twice daily, respectively. Thus, these doses fulfilled the prespecified criteria for MTD. In most cases, elevated CK was associated with myalgia. However, some patients reported myalgia and muscle spasm without CK elevation. Treatment-emergent CK elevation resolved within 4 to 8 weeks of drug discontinuation. No concurrent renal dysfunction was observed in any patient. Of the patients with CK elevation, eight resumed treatment on a reduced dose without recurrence. Eight of 19 patients with DLTs also experienced grade 3/4 AEs including increased aspartate aminotransferase, alanine aminotransferase, or myoglobin; muscular weakness; and myositis. No clinically significant changes in CK-MB suggestive of cardiac muscle injury were noted. In three cases, the DLTs were reported as rhabdomyolysis, primarily based on elevated blood CK \pm myoglobin levels without evidence of renal dysfunction. CK elevation in these patients resolved following discontinuation of sonidegib. No additional therapy was required in one patient—the other two patients received sodium chloride (n = 1) or furosemide (n = 1). Treatment with sonidegib was not resumed in these patients.

Pharmacokinetics

PK parameters were calculated for 102 patients based on the single-dose PK run-in and for 82 patients on day 15 of daily dosing. Mean sonidegib plasma concentration-time profiles following the PK run-in period prior to initiating continuous dosing are presented (Supplementary Fig. S2). Relevant PK parameters derived from the plasma concentration-time curves on PK run-in and day 15 of cycle 1 are summarized in Table 3. Sonidegib was absorbed after oral administration, with a median T_{max} of 2 hours (range 1–48 hours) for all dosing regimens and doses combined. Sonidegib plasma exposure (C_{max} and AUC) after single-dose administration increased dose proportionally from 100 to 400 mg and less than dose proportionally above 400 mg. After repeated once-daily dosing from 100 to 3000 mg, C_{max} and AUC on cycle 1, day 15 increased approximately dose proportionally up to 400 mg and less than dose proportionally above 400 mg. After twice-daily dosing from 250 to 750 mg, C_{max} and AUC on cycle 1, day 15 increased less than dose proportionally. Twice-daily dosing resulted in higher systemic exposures compared with the equivalent once-daily regimen. The 7-day PK run-in phase implemented in this study was not long enough to allow for accurate estimation of the terminal half-life ($t_{1/2}$), oral apparent clearance, or volume of distribution using noncompartmental methods. Based on the trough plasma concentration over time in patients monitored for a sufficiently long period without dose changes, steady state seemed variable and was achieved after 2 to 24 weeks of repeated dosing, with a median accumulation of 16-fold across the dose groups based on C_{min} . The estimated median effective elimination $t_{1/2}$ of sonidegib, calculated on the basis of the accumulation ratio, was ≈ 11 days. The interpatient coefficients of variation (CVs) for day 15 C_{max} and AUC were 39% to 113% and 33% to 122%, respectively, across the dose range of 100 to 3000 mg/day for all dosing regimens. At the MTD of 800 mg once daily and 250 mg twice daily, the day 15 exposures were similar, with CVs for

C_{\max} of 54% and 44% and AUC of 50% and 33%, respectively. The median accumulation ratio in 11 patients treated at 800 mg once daily was 16-fold. Increasing sonidegib dose and exposure were associated with increased odds of grade 3/4 CK elevation (Fig. 1, Supplementary Fig. S3).

Target Inhibition

Sonidegib treatment caused a reduction in GLI1 mRNA expression in tumor and skin (Fig. 2). Target inhibition in the tumor, as measured by GLI1 expression, was more pronounced than in the skin when both tissues were available for analyses (Supplementary Fig. S4). In general, the degree of target inhibition increased in a dose- and exposure-dependent manner, consistent with the utility of GLI1 expression as a pharmacodynamic marker for Hh pathway activation. However, in the limited number of samples analyzed, the reduction in GLI1 expression did not correlate with tumor response (data not shown).

Antitumor Activity

Ninety-nine patients (96%) were evaluable for tumor response. Partial tumor responses were observed over the dose range of 100 to 1500 mg. Six of 16 patients with BCC (37.5%) and three of nine patients with MB (33%) achieved objective tumor responses (partial or complete response) according to RECIST and FDG-PET (Supplementary Table S2). In the 3 patients with MB with a PR, who were treated at 200, 800, and 1500 mg once daily, duration of response ranged from 4 to 8 months. One patient with MB, aged 25 years, with largely metastatic bone disease, did not have RECIST-measurable lesions; hence FDG-PET was used to monitor treatment effect. The metabolic PR in this patient, maintained for 8 months, was associated with symptomatic improvement (reduction in bone pain). A patient with locally

infiltrating BCC achieved a histologic complete response confirmed by multiple biopsies of the tumor and surrounding tissue after treatment at 400 mg twice daily (Fig. 3A). PRs were also observed in five patients with locally advanced or metastatic BCC (spread to the lungs), treated at 100, 800, or 1000 mg once daily and 250 mg twice daily (Fig. 3B and 3C). Interestingly, the tumor burden of the patient who achieved a PR at 250 mg twice daily continued to improve for several months after treatment discontinuation. In patients with BCC and MB, there was a strong association between tumor response and Hh pathway activation, as determined by a five-gene Hh signature RT-PCR assay (Supplementary Table S2) (18). Best overall response of stable disease (SD) was observed in 24 patients (23%), with duration of SD > 6 months in three patients with lung adenocarcinoma, spindle cell sarcoma, and BCC.

DISCUSSION

Continuous daily oral administration of sonidegib exhibited an acceptable safety profile, exposure-dependent target inhibition, and antitumor activity. The vast majority of AEs were mild to moderate in severity. Treatment-related AEs were manageable and reversible after discontinuation of drug. The majority of treatment-related AEs in this study have been similarly observed with other SMO inhibitors in phase 1 studies in patients with advanced solid tumors (3, 8). The toxicity profiles of these agents cannot be directly compared in the absence of head-to-head trials; however, the most commonly reported AEs in >10% across the agents include muscle spasms, dysgeusia, fatigue, and alopecia (3, 8).

Current understanding of the role for Hh signaling suggests that the observed slowly evolving diffuse alopecia, dysgeusia, and muscle-related events are likely mechanistic on-target toxicities (21-23). SMO inhibitors have been shown to induce muscle contraction and muscle

fiber twitching in primary human muscle cells, which is thought to be due effects on calcium influx, thus providing a potential mechanism for the muscle spasms observed in patients treated with sonidegib in this study (23). Reversible dose-limiting CK elevation of skeletal muscle origin (based on total CK/CK-MB ratio) occurred in 18% of patients across all doses (< 10% at the MTD, 800 mg once daily), with no evidence of cardiac muscle injury. Overall, hyperCKemia (without evidence of renal impairment) was reported in \approx 46% of patients with normal CK at baseline. Six patients with CK elevation also had grade 3/4 increases in serum transaminases without significant changes in other liver function tests, thus suggesting skeletal muscle origin. High drug exposure was associated with increased odds of grade 3/4 CK elevations (Fig. 1, Supplementary Fig. S3). Although resolution of CK levels was slower than expected for the known half-life of CK, it was not entirely consistent with the long half-life of sonidegib. Some patients had resolution of CK despite maintaining high drug concentrations. Additionally, recurrence was not observed on retreatment at a reduced dose. For the three patients with DLTs documented as rhabdomyolysis, CK elevation resolved following discontinuation of treatment with supportive care (sodium chloride or furosemide in two of the three patients). Furosemide was administered as a precaution, apparently to boost urinary output in one patient, though there was no evidence of impaired renal function. Not surprisingly, there was no clear relationship between the incidence of muscle cramps/spasms and hyperCKemia, as many patients experience muscle cramps/spasms without CK elevation following SMO inhibitor treatments (3, 8). Other drugs with potential to cause toxic myopathy should be used in caution with SMO inhibitors (24).

The underlying reason for the relatively long half-life of sonidegib is unknown, although tight tissue and/or plasma protein binding can be speculated. High affinity protein binding was also

shown to contribute to the long half-life (> 7 days) of the SMO inhibitor vismodegib—a methanesulfonyl benzamide identified in a high-throughput screen (25). Sonidegib does not exhibit a time-dependent PK profile. The drug accumulation pattern over time and extent of accumulation at steady state are consistent with in vitro data showing lack of induction or time-dependent inhibition of CYP enzymes (10). Sonidegib displayed nonlinear pharmacokinetics at higher doses, likely due to solubility-limited absorption, and not due to dose-dependent metabolism as shown by parallel decline of the plasma concentration profile across the dose range. Solubility-limited absorption also contributed to the nonlinear pharmacokinetics observed for vismodegib, however, slow metabolic elimination was also a factor (25). Although twice-daily dosing provided a higher systemic exposure than equivalent once-daily doses, it did not appear to offer a clinically meaningful advantage over the once-daily regimen in this study. Therefore, the once-daily dosing regimen is currently recommended for further studies with sonidegib. However, the twice-daily dosing regimen may be considered in situations where a faster time to steady-state systemic concentration is desirable.

This proof-of-concept study demonstrated that sonidegib induced target inhibition and antitumor activity at well-tolerated drug exposures in patients with BCC and MB, tumor types known to harbor activating mutations (2). Sonidegib exhibited dose- and exposure-dependent inhibition of GLI1 in tumor and normal skin biopsies. GLI1 inhibition at maximum drug exposure at steady state is expected to be higher than that observed at the end of cycle 1. Although GLI1 inhibition in other tumors was comparable to BCC (Supplementary Fig. S4), no objective responses were reported in these tumors. Similarly, GLI1 stromal expression in a patient with rectal cancer treated with saridegib in a phase 1 study was reduced (8); however, this patient did not respond to treatment. The lack of response in these patients is most

probably due to differences in the tumor dependency on Hh signaling (ie, ligand-dependent versus ligand-independent). In the case of ligand-dependent tumors, other factors and signaling pathways may be involved in tumorigenesis—therefore, inhibition of Hh signaling alone may not be enough to induce a response. In phase 1 studies, both saridegib and vismodegib caused a reduction in GLI1 levels in approximately 74% of normal skin biopsies analyzed (3, 8). Taken together, these data suggest that GLI1 is an ideal marker for SMO inhibitor therapy, but not a marker for tumor response. Molecular alterations in other Hh pathway components in the patients who responded are unknown as mutational analyses were not conducted in this study; however, Hh pathway activity was assessed using the five-gene Hh signature assay, an RT-PCR-based assay, in fresh-frozen paraffin-embedded tumor samples—a strong association between tumor response and activated Hh pathway was observed in patients with BCC and MB (18, 19).

Similar responses in patients with advanced BCC (29-58%) have been observed in other phase 1 and 2 studies of SMO inhibitors (3, 4). The wide range of responses in these studies may be due in part to differences in patient populations and the methods of tumor evaluation across studies. In particular, assessment of response in BCC is confounded by the presence of residual scarring or fibrosis, making the standard provisions of RECIST sub-optimal.

To date, responses in MB have been reported only for sonidegib and vismodegib (3, 18, 26-29). Importantly, all responses occurred in patients with Hh-activated MB (18, 26-29).

Complete and partial responses have been observed in patients with MB in our study and in a phase 1/2 study of sonidegib in children with tumors thought to be dependent on Hh signaling (phase 1) and children and adults with Hh-activated MB (18). A dramatic but transient regression of systemic metastatic disease (primarily in the bone) was observed in an adult

patient treated with vismodegib in the first-in-man phase 1 study and three of 20 adult patients achieved sustained responses in a phase 2 study in recurrent MB (3, 27, 28). Antitumor activity was also observed in one pediatric patient with Hh-activated MB treated with vismodegib in a phase 1 study (29).

In conclusion, sonidegib treatment at the MTD of 800 mg daily and 250 mg twice daily was well tolerated and demonstrated dose- and exposure-dependent target inhibition. The antitumor activity in BCC and MB and mechanism-based toxicities observed demonstrate that sonidegib effectively inhibits Hh signaling. These results support the ongoing development of single-agent sonidegib for treatment of advanced BCC and relapsed MB, and further exploration in combination therapies in other cancers (30-33).

Acknowledgments

We thank Pat O'Rourke from the Cancer Therapy and Research Center at The University of Texas, Lea Felderer from the University Hospital of Zürich, and Marta Beltran, Rodrigo Dienstmann, Irene Braña, Guillem Argiles, and Gemma Sala from Vall d'Hebron Institut d'Oncologia in Barcelona and Vicente Garcia-Patos from the Department of Dermatology, Hospital Universitari Vall d'Hebron in Barcelona for patient care and data collection. We would also like to thank Corinne Emotte, Thad Sharp, and Douglas Robinson from Novartis Pharmaceuticals Corporation for sample analysis. Medical editorial assistance was provided by Jillian Brechbiel, PhD, and Karen Miller-Moslin, PhD. Financial support for editorial assistance was provided by Novartis Pharmaceuticals Corporation.

The Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center, San Antonio, Texas, is also funded by the Cancer Center Support grant P30CA054174.

The University of Pittsburgh Cancer Institute shared resources that are supported in part by award P30CA047904 were used for this project. The UPCI-Clinical Translational Research Center supported by the Clinical Translational Science Institute under the award NIH/NCRR/CTSA Grant UL1 RR024153 was used for this project.

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TABLES

Table 1. Demographic Summary and Disease Characteristics at Baseline

Baseline Characteristics	All Patients (n = 103)
Age, median years (range)	59.0 (22–87)
Male sex, %	61.2
Primary site of cancer, n (%)	
Pancreas	19 (18.4)
Colorectal	18 (17.5)
Other GI tumors ^a	8 (7.8)
BCC	16 (15.5)
Lung	10 (9.7)
Medulloblastoma	9 (8.7)
Genitourinary tumors ^b	5 (4.9)
Breast	3 (2.9)
Cutaneous melanoma	3 (2.9)
Other ^c	12 (11.7)
Prior antineoplastic therapies, n (%)	
Surgery	91 (88.3)
Radiotherapy	47 (45.6)
Systemic therapy ^d	96 (93.2)
Prior systemic therapies ^d	
1	20 (19.4)
2	22 (21.4)
> 2	54 (52.4)
ECOG performance status, n (%)	
0	41 (39.8)
1	55 (53.4)
2	7 (6.8)

Abbreviations: BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal.

^a Other GI tumors included cholangiocarcinoma (4), stomach (1), gall bladder (1), esophageal (1), and small intestine (1).

^b Genitourinary tumors included cervix (1), ovary (1), endometrial (1), prostate (1), and renal (1).

^c Other included leiomyosarcoma (2), germ cell (2), mesothelioma (2), Merkel cell carcinoma (1), spindle cell carcinoma (1), osteosarcoma (1), adenocarcinoma of unknown primary (1), ciliary body melanoma (1), and ampulloma (1).

^d Included chemotherapy, hormonal therapy, immunotherapy, and targeted therapy (one patient with BCC was previously treated with the topical formulation of sonidegib).

Table 2. Most Common Adverse Events (All Grades, $\geq 5\%$ Incidence) Suspected to Be Related to Sonidegib Treatment

	Once-Daily Doses, mg							Twice-Daily Doses, mg			
Total Adverse Events (%) <i>Grade 3/4 (%)^a</i>	100 (n = 6)	200 (n = 6)	400 (n = 5)	800 (n = 26)	1000 (n = 11)	1500 (n = 9)	3000 (n = 10)	250 (n = 14)	400 (n = 8)	750 (n = 8)	All (n = 103)
Gastrointestinal toxicity											
Nausea	3	1	0	4	3	4	2	3	1	5	26 (25.2)
Dysgeusia	1	1	0	5	3	3	5	6	3	3	30 (29.1)
Anorexia	2	1	1	8 1	4	0	4	5	3	2	30 (29.1) 1 (1.0)
Vomiting	1	1	0	3	1	1	1	2	1	2	13 (12.6)
Diarrhea	0	0	0	2	0	0	1	1	1	2	7 (6.8)
Constipation	0	1	0	1	1	0	1	0	0	2	6 (5.8)
Muscle spasms	2	2	0	9	3	4	0	5	4	4	33 (32.0)
Myalgia	0	1	0	4	3 1	2	2	3	0	2	17 (16.5) 1 (1.0)
Blood CK increased	1	1	0	7 2	4 2	3 3	4 3	3 2	4 2	6 5	33 (32.0) 19 (18.4)
Increased transaminases^b	0	0	0	2	0	2	2 2	6 2	2 1	1 1	15 (14.6) 6 (5.8)
Fatigue/asthenia	5	2	0	6 1	4 1	3 1	0	4	3	1	28 (27.2) 3 (2.9)
Alopecia	1	1	0	4	1	2	1	1	2	0	13 (12.6)
Lethargy	0	0	0	3	1	0	1	1	0	1	7 (6.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

^a Italicized numbers indicate grade 3/4 adverse events.

^b Includes increased AST or ALT.

Table 3. Summary of Sonidegib PK Parameters After a Single Dose on Day 1 of PK Run-in and Repeated Doses on Day 15 of Cycle 1

PK Run-in				
Dose, mg	N	C_{max}, ng/mL Mean (SD; CV%)	AUC_{0-168h}, ng × h/mL Mean (SD; CV%)	T_{max}, h^a Median (min–max)
100 once daily	6	85.8 (52.3; 61)	1880 (1150; 61)	2 (1–24)
200 once daily	6	160 (115; 72)	3670 (2130; 58)	2 (2–48)
400 once daily	5	267 (239; 90)	7450 (8530; 115)	4 (4–4)
800 once daily^b	25	430 (381; 89)	7870 (6950; 88)	4 (1–27)
1000 once daily	11	322 (258; 80)	7400 (6340; 86)	2 (1–4)
1500 once daily	9	376 (199; 53)	12,600 (7110; 56)	4 (2–24)
3000 once daily	10	429 (237, 55)	11,800 (11,200; 95)	2 (1–8)
250 twice daily^b	14	150 (111; 74)	3, 20 (2320; 72)	2 (1–4)
400 twice daily	8	334 (300; 90)	7530 (7020; 93)	4 (2–4)
750 twice daily	8	226 (180; 80)	6920 (7110; 103)	3 (1–23)
Day 15, cycle 1				
Dose, mg	n^c	C_{max}, ng/mL Mean (SD; CV%)	AUC_{0-24h}, ng × h/mL^c Mean (SD; CV%)	T_{max}, h^a Median (min–max)
100 once daily	3	155 (63.4; 41)	2690 (1340; 50)	4 (2–6)
200 once daily	5	269 (163; 61)	5920 (3890; 66)	4 (0-6)
400 once daily	4	558 (286; 51)	10,200 (5880; 58)	13 (1–24)
800 once daily^b	20	840 (457; 54)	12,800 (6350; 50)	2 (1–6)
1000 once daily	8	1230 (1400; 113)	15,200 (18,500; 122)	4 (2–6)
1500 once daily	8	1320 (657; 50)	27,400 (14,300; 52)	5 (2–24)
3000 once daily	6	1670 (1050, 62)	24,600 (8770; 36)	3 (0–21)
250 twice daily^b	13	807 (353; 44)	14,500 (4780; 33)	2 (0–6)
400 twice daily	7	864 (333; 39)	13,800 (6390; 46)	2 (0–8)
750 twice daily	8	1570 (1020; 65)	26,900 (17,300; 64)	4 (0–8)

Abbreviations: AUC_{0-168h} , area under the plasma concentration-time curve from time zero to 168 hours; AUC_{0-24h} , area under the plasma concentration-time curve from time zero to 24 hours; C_{max} , maximum plasma drug concentration; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; T_{max} , time to reach C_{max} . AUC_{0-24h} for twice-daily doses are calculated as $2 \times AUC_{0-12h}$.

^a Values are median (range) and arithmetic mean (SD; CV%) for all other parameters.

^b Bold values represent maximum tolerated dose for once-daily and twice-daily doses.

^c AUC analysis on cycle 1, day 15 included 3, 3, 4, 16, 6, 3, 4, 12, 5, and 6 patients from the 100, 200, 400, 800, 1000, 1500, 3000 mg once-daily and 250, 400, and 750 mg twice-daily dose cohorts, respectively.

FIGURE LEGENDS

Fig. 1. Relationship between sonidegib exposure and creatine kinase (CK) elevation.

Sonidegib area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}) on day 15 of cycle 1 was plotted for each patient by dose cohort. Incidences of CK elevation were noted for each patient. Incidence of grade 3/4 CK elevation was associated with increased sonidegib exposure. Grey-filled diamonds indicate patients without grade 3 or 4 CK elevation; black-filled circles indicate patients who experienced grade 3 or 4 CK elevation. Black solid line indicates mean AUC.

Fig. 2. Glioma-associated oncogene homolog 1 (GLI1) fold change and percent inhibition in normal skin by dose cohort after sonidegib treatment. GLI1 expression was analyzed in patient skin specimens before and after treatment with sonidegib. Fold change from baseline was determined and plotted by dose cohort. Sonidegib treatment induced a dose-dependent decrease in GLI1 expression. Dotted lines represent 50%, 60%, and 90% mean inhibition.

Fig. 3. Responses in patients with basal cell carcinoma (BCC) treated with sonidegib. (A) Immunohistochemistry (IHC) of a 76-year-old male patient with BCC treated with 400 mg twice daily. Histologically confirmed complete response was noted after 4 months of treatment. Photographs (B) and IHC (C) of BCCs in a 55-year-old male patient with Gorlin syndrome treated with 800 mg once daily. Partial response was observed after \approx 6 months. Circles in (A) highlight the presence or absence of tumor tissue; arrows in (A) highlight fibrosis.

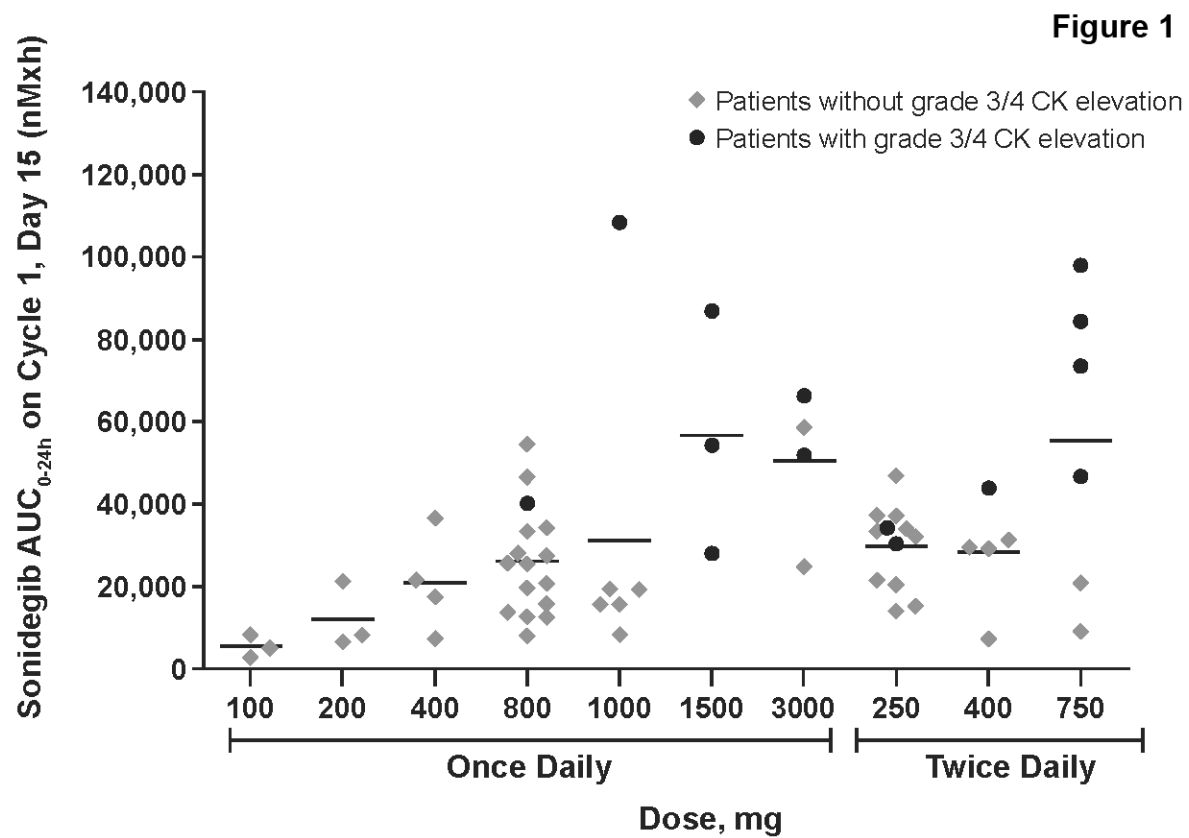


Figure 2

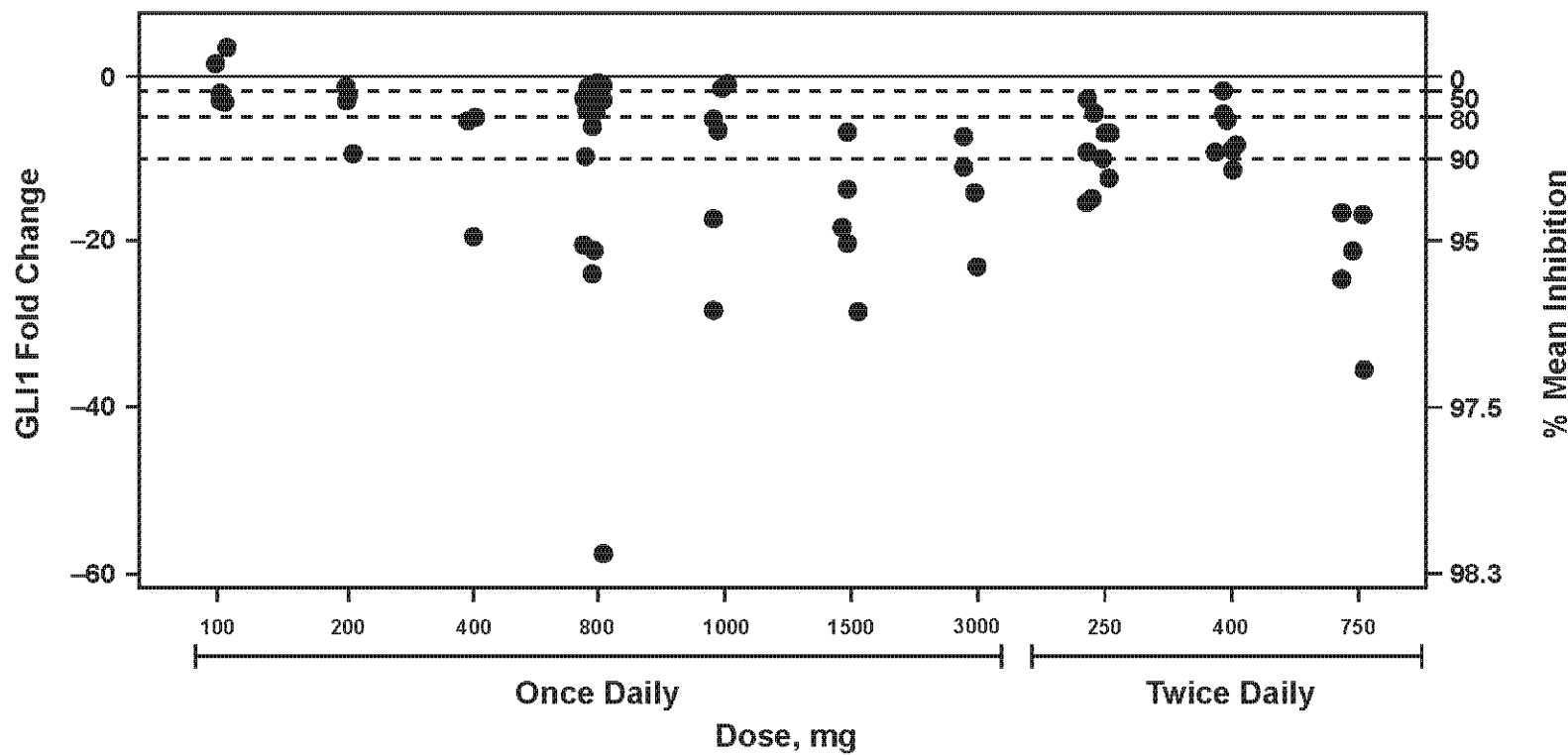


Figure 3

